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<p>(21) International Application Number: PCT/DK88/00188</p> <p>(22) International Filing Date: 17 November 1988 (17.11.88)</p> <p>(31) Priority Application Number: 8728051</p> <p>(32) Priority Date: 1 December 1987 (01.12.87)</p> <p>(33) Priority Country: GB</p> <p>(71) Applicant (for all designated States except US): LEO PHARMACEUTICAL PRODUCTS LTD. A/S (LØVENS KEMISKE FABRIK PRODUKTION-SAKTIESELSKAB) [DK/DK]; Industriparken 55, DK-2750 Ballerup (DK).</p> <p>(72) Inventors; and (75) Inventors/Applicants (for US only) : AHN FELT-RØNNE, Ian [DK/DK]; Langerødvej 33, DK-3480 Fredensborg (DK). HANSEN, Erik, Torngård [DK/DK]; Asmundshøj 457, DK-3480 Fredensborg (DK). KIRSTEIN, Dorte [DK/DK]; Lehwaldsvej 3, 6F, DK-2800 Lyngby (DK). NIELSEN, Ole, Bent, Tværmose [DK/DK]; Risagervej 4, DK-2720 Vanløse (DK). RACHLIN, Schneur [DK/DK]; Sønder søvej 17,</p>		<p>DK-3500 Værløse (DK).</p> <p>(74) Agent: RYDAHL KRISTENSEN, P.; Leo Pharmaceutical Products, Industriparken 55, DK-2750 Ballerup (DK).</p> <p>(81) Designated States: AT (European patent), AU, BE (European patent), CH (European patent), DE (European patent), DK, FR (European patent), GB (European patent), IT (European patent), JP, KR, LU (European patent), NL (European patent), SE (European patent), US.</p> <p>Published With international search report.</p>
<p>(54) Title: SUBSTITUTED QUINOLINES</p> <div data-bbox="467 1276 1360 1438" data-label="Chemical-Block"> <p style="text-align: right;">(I)</p> </div> <p>(57) Abstract</p> <p>The present invention relates to hitherto unknown compounds of formula (I), in which formula (I) R₁ stands for hydrogen, straight or branched, saturated or unsaturated, unsubstituted or substituted C₁-C₃-alkyl, aryl or for ar-C₁-C₄-alkyl, aryl or ar being unsubstituted or substituted phenyl, R₂, R₃, R₄, R₅, R₆ and R₇ are the same or different and stand for hydrogen, halogen, pseudo halogen, cyano, nitro, amino, carboxy, carbalkoxy, carbamyl, hydroxy, alkyl, alkoxy; n and m are the same or different and stand for an integer from 0-6; provided that n cannot be zero when A stands for carboxy and X and Q both stand for a bond; X stands for a bond or for O, S, S(O), S(O)₂ or for NR₈ where R₈ is defined as R₁ above; Q stands for a bond or for straight or branched, C₁-C₆-alkylene; A stands for an acidic group, e.g. for carboxy, 1H-tetrazolyl, a sulphonic acid group, a sulfamyl group, a sulphinic acid group or a hydroxamic acid group. The present compounds are of value in the human and veterinary practice as lipoxigenase inhibitors and/or leukotriene antagonists.</p>		

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SUBSTITUTED QUINOLINES

The present invention relates to hitherto unknown compounds useful in the human and veterinary therapy, to
5 pharmaceutically acceptable salts thereof, to bioreversible derivatives thereof, to methods for producing said new compounds, to pharmaceutical compositions containing the new compounds, to dosage units of the compositions, and to
10 methods of treating patients using said compositions and dosage units.

It has recently been discovered that leukotrienes, which are formed via the 5-lipoxygenase pathway of arachidonic acid metabolism, are implicated in a variety of pathophysiologic functions, such as bronchoconstriction,
15 plasma exudation, coronary artery spasm, leukocyte chemotaxis and neutrophil degranulation (1). It is therefore of considerable interest to develop compounds which inhibit 5-lipoxygenases and thereby the production of leukotrienes, or antagonize the effects of leukotrienes.

20 German patent application DE 3607 382 (corresponding to United Kingdom patent application No. 8604183) describes a series of pyridylmethoxy or -methyl-thio substituted N-substituted aniline derivatives with activities as lipoxygenase inhibitors and/or leukotriene antagonists. The
25 N-substituent in these compounds may be substituted or unsubstituted aryl or aralkyl.

Now it has surprisingly turned out that introduction of one of a number of acidic groups into such N-substituents results in compounds with an even more pronounced effect.

30 Furthermore, it has been found that in the presence of such acidic groups also compounds which are not anilines, but in which the nitrogen atom has been separated from the phenyl group with a carbon chain are potent compounds.

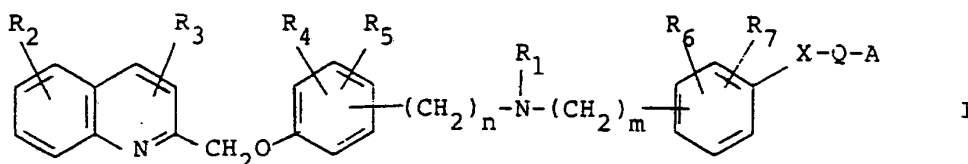
Moreover, these compounds are more specific agents,

(1) P.J. Piper and M.N. Samhoun, Br.Med.Bull. 43 (1987) 297.

as their leukotriene antagonistic activity is much more pronounced than their activity as lipoxygenase inhibitors.

Also, the present compounds are well absorbed after enteral administration.

5 The present compounds have the formula I



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in which formula I R_1 stands for hydrogen, straight or branched, saturated or unsaturated, unsubstituted or substituted C_1 - C_8 -alkyl, aryl or for ar- C_1 - C_4 -alkyl, aryl or ar being unsubstituted or substituted phenyl, the above
 15 substitution being one or more of the following substituents: halogen, pseudo halogen, such as trifluoro methyl, cyano, nitro, amino, carboxy, carbalkoxy, carbamyl, hydroxy, alkyl, alkoxy; R_2 , R_3 , R_4 , R_5 , R_6 and R_7 are the same or different and stand for hydrogen, halogen, pseudo halogen,
 20 cyano, nitro, amino, carboxy, carbalkoxy, carbamyl, hydroxy, alkyl, alkoxy; n and m are the same or different and stand for an integer from 0-6; provided that n cannot be zero when A stands for carboxy and X and Q both stand for a bond; X stands for a bond or for O , S , $S(O)$, $S(O)_2$ or for NR_8 where
 25 R_8 is defined as R_1 above; Q stands for a bond or for straight or branched, C_1 - C_6 -alkylene; A stands for an acidic group, e.g. for carboxy, 1H-tetrazolyl, a sulphonic acid group, a sulfamyl group, a sulphinic acid group or a hydroxamic acid group.

30 Among the preferred compounds of the invention are those of formula I, in which $-X-Q-A$ stands for a carboxy- C_1 - C_6 -alkoxy or a 1H-tetrazolyl group.

The present salts of the compounds of formula I may be formed with pharmaceutically acceptable inorganic or
 35 organic acids, such as hydrochloric, hydrobromic and hydroiodic acid, phosphoric acid, sulphuric acid, nitric acid, p-toluenesulphonic acid, methanesulphonic acid, formic acid, acetic acid, propionic acid, citric acid, tartaric acid, and maleic acid, without these examples being considered

limiting for the invention.

The present salts of the compounds of formula I may also be formed with pharmaceutically acceptable, inorganic or organic bases. As examples of salts formed with pharmaceutically acceptable, non-toxic bases, mention may be made of alkali metal salts and alkaline earth metal salts, such as lithium, sodium, potassium, magnesium, calcium salts, as well as salts with ammonia and suitable non-toxic amines, such as C₁-C₆-alkylamines, e.g. triethylamine, C₁-C₆-alkanolamines, e.g. diethanolamine or triethanolamine, procaine, cycloalkylamines, e.g. dicyclohexylamine, benzylamines, e.g. N-methylbenzylamine, N-ethylbenzylamine, N-benzyl-β-phenethylamine, N,N'-dibenzylethylenediamine or dibenzylamine, and heterocyclic amines, e.g. morpholine, N-ethylpiperidine and the like.

Even if the present compounds are well absorbed after enteral administration, in some cases it can be advantageous to prepare suitable bioreversible derivatives of compounds of the invention, i.e. to prepare so-called prodrugs, preferably derivatives, the physiochemical properties of which leads to improved solubility at physiological pH and/or absorption of the compound in question.

Such derivatives are for instance esters of N-hydroxymethyl derivatives of compounds of the invention, such compounds being prepared by reaction of a secondary aminefunction of compounds of the invention with form-aldehyde (2,3,4,5) followed by reaction with a suitable acidic compound or activated derivatives of such compounds,

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- (2) R.G. Kallen and W.P. Jencks, J. Biol. Chem. 241 (1966) 5864.
- (3) C.J. Martin and M.A. Marini, J. Biol. Chem. 242 (1967) 5736.
- (4) M. Levy and D.E. Silberman, J. Biol. Chem. 118 (1937) 723.
- (5) S. Lewin and D.A. Humphany, J. Chem. Soc. B (1966) 210.

for instance with bisulfite (6), N,N-dimethylglycine, N,N-diethyl- β -alanine, or phosphoric acid (7), but other suitable acids which form bioreversible derivatives with desirable physicochemical properties can be used as well.

5 Further examples include esters formed with the acidic function in the molecule, such as acyloxyalkyl, alkoxy-carbonyloxyalkyl or aminoacyloxyalkyl esters, which are readily hydrolyzed in vivo or in vitro.

Among the above esters the following are preferred:
10 alkanoyloxymethyl with from 3 to 8 carbon atoms, 1-alkanoyloxy)ethyl with from 4 to 9 carbon atoms, alkoxy-carbonyloxy-methyl with from 3 to 6 carbon atoms, 1-(alkoxy-carbonyloxy)-ethyl with from 4 to 7 carbon atoms, and α -aminoalkanoyloxy-methyl with from 2 to 6 carbon atoms.

15 Other preferred esters are lactonyl esters, e.g. 3-phthalidyl, 4-crotonolactonyl or γ -butyrolacton-4-yl esters.

Also within the scope of the invention are methoxymethyl, cyanomethyl, or mono- or dialkyl substituted amino-
20 alkyl esters, e.g. 3-dimethylaminoethyl, 2-diethylaminoethyl, or 3-dimethylaminopropyl esters.

In particular, such esters are preferred which are well absorbed upon enteral administration and during or after the absorption are hydrolysed to the compounds of
25 formula I.

These examples are not to be considered as limiting for the invention, and other suitable methods to improve the physicochemical properties and solubility of the compounds concerned can be used as well.

30 Metabolites of arachidonic acid include prostaglandins and leukotrienes. Both of these two groups of metabolites are important in the pathophysiology of inflammatory and allergic reactions. Many inhibitors of prostaglandin synthesis are known and are being used as anti-inflammatory

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(6) B.C. Jain, B.H. Iyer, and P.C. Guha, Science and Culture 11 (1946) 568.

(7) S.A. Varia, S. Schuller, K.B. Sloan and V.J. Stella, J. Pharm. Sci., 73 (1985) 1068 and following papers.

agents (8), but relatively few leukotriene inhibitors are presently known, and they are generally not clinically acceptable. The first step in the biochemical synthesis of all leukotrienes is the peroxidation at the 5-carbon atom of arachidonic acid. This reaction is catalyzed by the enzyme 5-lipoxygenase, present mainly in leukocytes. Leukotriene B₄ is one of the most potent chemoattractants for polymorphonuclear leukocytes, and at the same time causes aggregation and degranulation of these inflammatory cells. It is thus a potent pro-inflammatory hormone. Leukotriene C₄, D₄, and E₄ together comprise the agent known previously as "slow-reacting substance of anaphylaxis" (SRS-A), which is three orders of magnitude more potent than histamine in causing bronchoconstriction, and also regulates microvascular smooth muscle contractility and permeability. It is therefore a mediator of asthmatic, allergic and inflammatory reactions.

Inhibition of 5-lipoxygenase thus leads to a decrease in the formation of all of these inflammatory and allergic mediators. This has very important clinical implications, as specific 5-lipoxygenase inhibitors and leukotriene antagonists are of potential interest in the therapy of asthma, allergy, rheumatoid arthritis, spondyloarthritis, gout, atherosclerosis, proliferative and inflammatory skin-disorders, such as psoriasis and atopic dermatitis, chronic inflammatory bowel disease, and other inflammatory conditions, vasospasm associated with angina pectoris, pulmonary hypertension, cystic fibrosis, the adult respiratory distress syndrome, ischemic and reperfusion injury etc. (9). The identification of specific 5-lipoxygenase inhibitors and leukotriene antagonists is thus a novel approach with very wide implications for the treatment of a diversity of clinical disorders.

The following method was used to assay 5-lipoxygenase

(8) R.J. Flower, S. Moncada and J.R. Vane, in: The Pharmacological Basis of Therapeutics (1980), eds. A.G. Gilman, L.S. Goodman and A. Gilman), (Macmillan, New York) p. 682.

(9) E.J. Goetzl, D.G. Payan and D.W. Goldman, J. Clin. Immunol. 4 (1984) 79.

activity in vitro: Rat peritoneal cells were harvested by i.p. injection of 10 ml Hank's balanced salt solution (GIBCO, cat. No. 4025, U.S.A.) containing 12.5 U/ml sodium heparin (Leo, Denmark) in anaesthetized rats. The resulting cell suspension, which mainly contained macrophages, was transferred to a test tube and washed twice by centrifugation (200 g, 10 min.) and resuspended in Hank's balanced salt solution containing 0.5% bovine serum albumin (BSA) (Sigma Chem. Co., U.S.A.). The cells from 9 rats were finally resuspended in Hank's balanced salt solution (with BSA) containing 5 μ Ci [1-¹⁴C]arachidonic acid (The Radiochemical Centre, Amersham, U.K.) and incubated for 90 minutes at 37°C. This caused labelling of cell membrane phospholipids as radioactive arachidonic acid was incorporated in the 2-position of the glycerol moiety. Excess arachidonic acid was then removed by washing the cells twice as described above. The cells were finally resuspended in the same solution (without BSA) at 10⁷ cells/ml. 475 μ l of the cell suspension was preincubated at 37°C for 5 minutes with either 5 μ l dimethylsulphoxide (DMSO) (control tube), or 5 μ l of a drug solution in DMSO. Then 20 μ l of a mixture of equal volumes of the calcium ionophore A23187, 10⁻⁴M in ethanol (Calbiochem, U.S.A.), and 0.5 M CaCl₂ in water was added. The final concentration of A23187 was thus 2 x 10⁻⁶M, and of Ca⁺⁺ 8mM. After 5 minutes of incubation the tubes were transferred to an ice-bath and centrifuged for 10 minutes at 3,000 g (4°C). An aliquot of the supernatant was counted by liquid scintillation spectrometry in order to calculate the total radioactive release induced by A23187 in presence of drugs. A decrease in radioactive release was taken as indication of phospholipase A₂ inhibition. The supernatant was then extracted with ethyl acetate (2 ml), adjusted to pH 3 with 1 N HCl and further extracted with 2 ml ethyl acetate. The combined extracts were evaporated to dryness in vacuo, the residue was redissolved in a small volume of methanol and applied by means of a Desaga AutospotterTM to a silica-gel coated thin-layer plate fitted with a polar concentrating zone (Merck Art. 11798, Darmstadt, F.R.G.). The plates were

developed in the organic layer of the solvent mixture ethyl acetate/acetic acid/iso-octane/water (55:10:25:50). Radioactive spots were detected by autoradiography (AGFA-GEVAERT, Osray-RPI X-ray film, Belgium), and changes induced by drugs in the metabolic pattern of arachidonic acid were quantified by a laser densitometer (LKB, Ultrosan TM2202, Bromma, Sweden) in combination with an integrating computer (SP 4100, Spectra-Physics, San Jose, Ca., U.S.A.).

These cells produced measurable amounts of radioactive 6-keto-prostaglandin $F_{1\alpha}$, thromboxane B_2 , prostaglandin D_2 , hydroxyheptadecatrienoic acid (HHT) (all cyclooxygenase products), 5-hydroxyeicosatetraenoic acid (5-HETE) and leukotriene B_4 (both 5-lipoxygenase products).

When a compound produced according to one of the Examples 2, 8, 9, 11, 12, 13, 14, 16, 20, 21 or 22 at a final concentration of 10^{-6} M was added to the reaction mixture described above, a significant and specific decrease in the production of leukotriene B_4 and 5-HETE occurred. At the same time, a decrease in synthesis of the cyclooxygenase products HHT, prostaglandin D_2 , thromboxane B_2 and 6-keto-prostaglandin $F_{1\alpha}$ was not observed. This pattern of drug activity is indicative of truly specific 5-lipoxygenase inhibition.

Leukotriene antagonists may be identified by observing the contractions elicited in preparations of guinea-pig ileum strips suspended in a physiological buffer by addition of pure leukotriene D_4 (LTD_4) (10). The ileum strips are connected to an isotonic transducer, and the contractions are continuously recorded on a multichannel recorder.

Before addition of LTD_4 , atropine and indomethacin are added to the buffer in order to block any cholinergic or prostaglandinmediated contractile effects. Test compounds to be studied with respect to leukotriene antagonism are dissolved in DMSO and added to the organ bath 2 minutes prior to addition of LTD_4 at 10^{-9} M (final concentration), the final concentration of DMSO being 0.1%, a concentration which can be shown not to affect the ileum response to LTD_4 . The test

(10) I. Ahnfelt-Rønne, D. Kirstein and C. Kærgaard-Nielsen, European J. Pharmacol. 155 (1988) 117.

compounds may be added at various concentrations, often beginning at 10^{-6} M and then decreasing the concentration in case of antagonism.

When the compounds of the present invention were added to the ileum preparation before addition of LTD₄ a significant inhibition occurred of the specific LTD₄-induced contraction. In several cases this inhibition occurred at concentrations in the submicromolar range, e.g. with a compound according to one of the Examples 1 to 6 or 8 to 19 or 21 to 22 (all Examples except 7 and 20). On the other hand, contractions induced with histamine at 10^{-7} M were not inhibited by these compounds even at micromolar concentrations.

Leukotriene antagonists may be further characterized using guinea-pig tracheal strips instead of ileum strips (10). In this relevant in vitro model of human airways (11) tracheal strips are suspended in a physiological buffer containing indomethacin. A concentration-response curve to LTD₄ is generated in the presence and absence of the leukotriene antagonist. From these curves the potency of a leukotriene antagonist may be expressed as the pK_B value, the negative logarithm of the antagonist dissociation constant. The pK_B value is determined as $-\log([\text{antagonist}]/(\text{dose ratio} - 1))$, where the dose ratio is defined as EC₅₀ (presence of antagonist)/EC₅₀ (absence of antagonist) and EC₅₀ refers to the concentration of LTD₄ eliciting 50% of the maximum response to LTD₄ (12). This is the generally accepted way of expressing leukotriene antagonistic potency independent of LTD₄ concentration. pK_B values for the compounds according to the Examples 1, 9 and 10 were found to be 8.3, 9.5 and 8.4, respectively.

It is of importance to investigate the receptor binding properties of leukotriene antagonists in relation to

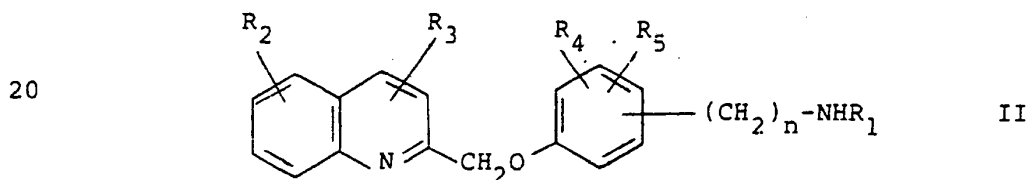
(11) R.M. Muccitelli, S.S. Tucker, D.W.P. Hay, T.J. Torphy and M.A. Wasserman, J. Pharmacol. Exp. Ther. 243 (1987) 467.

(12) R.F. Furchgott, in: Handbook of Experimental Pharmacology, vol 33 (1972), eds. O. Eichler, A. Farah, H. Herken and A.D. Welch (Springer Verlag, New York) p. 283.

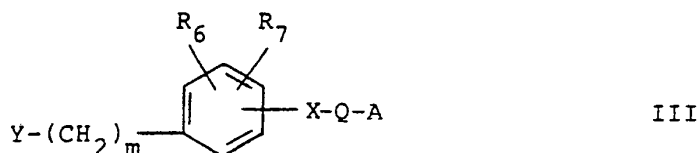
their pK_B values (13), i.e. to correlate antagonist receptor blocking with inhibition of smooth muscle contraction. Receptor binding studies may be performed with guinea-pig lung membranes in a direct competition assay between a
 5 leukotriene antagonist and [3H]LTD₄ for binding to the LTD₄ receptor (10,13). A pIC_{50} value is determined as the negative logarithm of the molar concentration of antagonist inhibiting [3H]LTD₄ binding by 50%. pIC_{50} values for the compounds according to the Examples 1, 9 and 10 were found
 10 to be 7.3, 8.1 and 7.5, respectively. These pIC_{50} values were observed to correlate with the antagonist pK_B values, proving that the inhibition of smooth muscle contraction by the present compounds in fact depends mechanistically on binding to the LTD₄ receptor.

15 The present invention also relates to a method for producing the present compounds.

In one embodiment, an amine of the formula II



in which R_1 , R_2 , R_3 , R_4 , R_5 and n have the above meanings,
 25 is reacted with a compound of the formula III



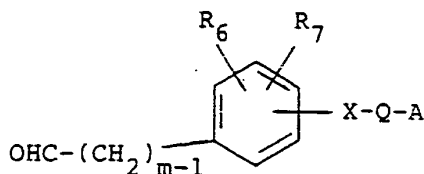
30 in which R_6 , R_7 , X , Q , A and m have the above meanings, and Y is capable of forming a "good leaving group", Y thus standing for e.g. a halogen atom, such as chlorine, bromine or iodine, or an alkyl- or arylsulphonyloxy group, but other
 35 leaving groups can be used as well, such as an alkylsulphate

- (13) S. Mong, H.-L. Wu, M.O. Scott, M.A. Lewis, M.A. Clark, B.M. Weichman, C.M. Kinzig, J.G. Gleason and S.T. Crooke, J. Pharmacol. Exp. Ther. 234 (1985) 316.

group, a chlorosulphonyloxy group, an alkylsulphite group, a mono- or dialkylphosphate group or a nitrate group, to form a compound of the formula I.

The reaction is performed in a suitable inert organic solvent, such as methanol, ethanol, dimethylformamide or hexamethyl phosphoric triamide, but other solvents can be used as well; the reaction is performed at a temperature about or above room temperature, up to the boiling point of the solvent used. In some cases it can, however, be convenient to cool the reaction mixture below room temperature, depending on the nature of the compound of the formula III used. The reaction is also conveniently performed in the presence of an organic base, such as pyridine, triethylamine, sodium methanolate or sodium ethanolate or in the presence of a suitable inorganic base, such as an alkali-metal hydroxide, an alkalimetal carbonate or an alkalimetal hydrogen carbonate, but other bases can be used as well. The crude reaction products of the formula I are collected by filtration, if convenient after dilution with e.g. water, or are extracted from the reaction mixture with a suitable solvent, such as diethyl ether, ethyl acetate, dichloromethane or chloroform. The products are purified e.g. by recrystallization or by chromatography, if convenient after conversion to salts with suitable inorganic or organic acids as defined above.

In another embodiment, an amine of the formula II in which R_1 stands for hydrogen is converted to a compound of the formula I, in which R_1 stands for hydrogen by reductive alkylation, e.g. by reaction with a carbonyl compound of the formula IV



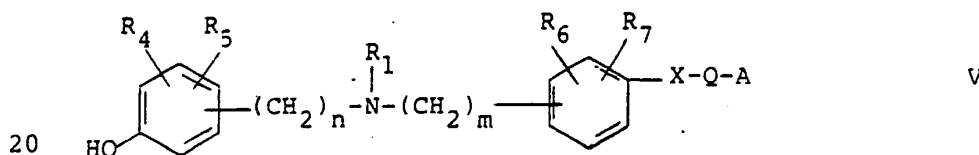
IV

in which R_6 , R_7 , X, Q, A and m have the above meanings, followed by hydrogenation in the presence of a suitable catalyst or by reduction e.g. with an alkalimetal boro-

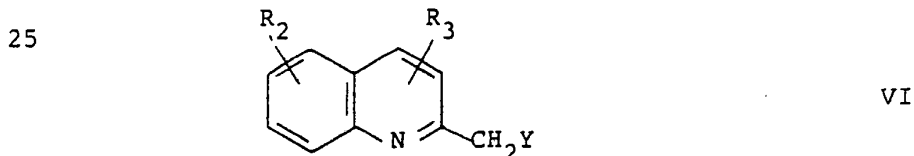
hydride. The hydrogenation or reduction can, if convenient, be performed simultaneously with the reaction with the carbonyl compound, that is, without isolation of the intermediary, so called Schiff-base.

5 The reaction is performed in a suitable inert organic solvent, such as methanol or ethanol, but other solvents can be used as well. The reaction is preferably performed at ambient temperature, but in some cases it is convenient to cool the reaction mixture below room temperature, or to heat
10 the reaction mixture above room temperature, up to the boiling point of the solvent used, depending on the nature of the reactants of the formulae II and IV used. The isolation and purification of the products can be performed as described above.

15 In still another embodiment a compound of the formula V



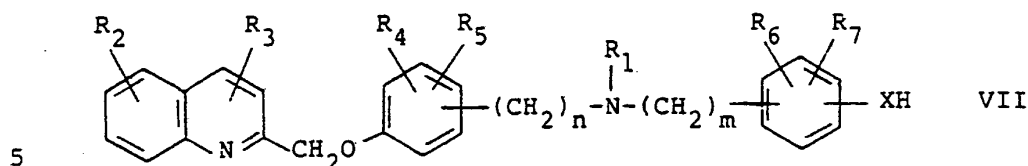
in which R_1 , R_4 , R_5 , R_6 , R_7 , X, Q, A, n and m have the above meanings, is reacted with a compound of the formula VI



30 in which R_2 , R_3 and Y have the above meanings, to form the desired compound of formula I.

The solvent and reaction conditions used are conveniently as described above for the alkylation of amines of the formula II, but other solvents and/or reaction
35 conditions can be used as well, depending on the nature of the compounds of formulae V and VI which are reacted.

In a further embodiment a compound of the formula VII



in which R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , R_7 , n and m have the above meanings, and X stands for O , S or NHR_8 , where R_8 has the above meanings, is reacted with a compound of the formula

10 VIII

Y-Q-A

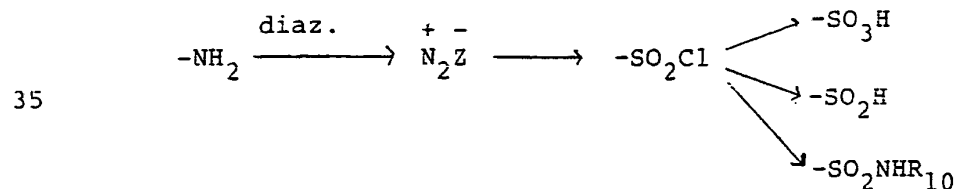
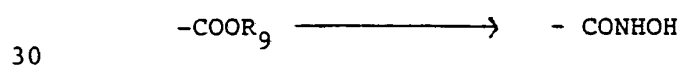
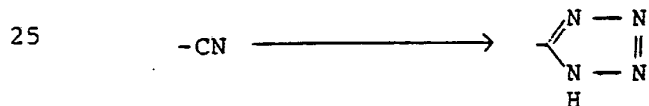
(VIII)

in which A , Q , and Y have the above meanings, to form the desired compound of formula I.

15 The solvent and reaction conditions used are conveniently as described above for the alkylation of amines of the formula II, but other solvents and/or reaction conditions can be used as well, depending on the nature of the compound of the formulae VII and VIII which are

20 reacted.

Additionally, the acidic functionalities A can be prepared according to the following general reaction schemes:



R_{10} having the same meanings as R_1 .

The present compounds are intended for use in pharmaceutical compositions which are useful in the treatment of the above mentioned diseases.

5 The amount required of a compound of formula (I) (hereinafter referred to as the active ingredient) for therapeutic effect will, of course, vary both with the particular compound, the route of administration and the mammal under treatment. A suitable dose of a compound of
10 formula (I) for a mammal suffering from e.g an inflammatory condition as defined hereinbefore is 0.5 to 100 mg per kilogram bodyweight, the most preferred dosage being 0.5 to 50 mg/kg of mammal bodyweight, for example 5 to 25 mg/kg; administered once or more times daily.

15 In the case of the treatment or prophylaxis of inflammatory airway conditions, a suitable anti-asthmatic dose of a compound of formula (I) is 1 μ g to 50 mg of compound per kilogram bodyweight, the most preferred dosage being 1 μ g to 10 mg/kg of mammal bodyweight, for example
20 from 1 μ g to 5 mg/kg.

While it is possible for an active ingredient to be administered alone as the raw chemical, it is preferable to present it as a pharmaceutical formulation. Conveniently, the active ingredient comprises from 0.1% to 100% by weight
25 of the formulation. Conveniently, dosage units of a formulation contain between 0.1 mg and 1 g of the active ingredient. For topical administration, the active ingredient preferably comprises from 1% to 2% by weight of the formulation but the active ingredient may comprise as
30 much as 10% w/w. Formulations suitable for nasal or buccal administration, (such self-propelling powder-dispensing formulations described hereinafter), may comprise 0.1 to 20% w/w, for example about 2% w/w of active ingredient.

By the term "dosage unit" is meant a unitary, i.e. a
35 single dose which is capable of being administered to a patient, and which may be readily handled and packed, remaining as a physically and chemically stable unit dose comprising either the active material as such or a mixture of it with solid or liquid pharmaceutical diluents or

carriers.

The formulations, both for veterinary and for human medical use, of the present invention comprise an active ingredient in association with a pharmaceutically acceptable carrier therefor and optionally other therapeutic ingredient(s). The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulations and not deleterious to the recipient thereof.

The formulations include those in a form suitable for oral, ophthalmic, rectal, parenteral (including subcutaneous, intramuscular and intravenous), intra-articular, topical nasal or buccal administration.

The formulations may conveniently be presented in dosage unit form and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing the active ingredient into association with the carrier which constitutes one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing the active ingredient into association with a liquid carrier or a finely divided solid carrier or both, and then, if necessary, shaping the product into the desired formulation.

Formulations of the present invention suitable for oral administration may be in the form of discrete units as capsules, sachets, tablets or lozenges, each containing a predetermined amount of the active ingredient; in the form of a powder or granules; in the form of a solution or a suspension in an aqueous liquid or non-aqueous liquid; or in the form of an oil-in-water emulsion or a water-in-oil emulsion. The active ingredient may also be administered in the form of a bolus, electuary or paste.

A tablet may be made by compressing or moulding the active ingredient optionally with one or more accessory ingredient. Compressed tablets may be prepared by compressing, in a suitable machine, the active ingredient in a free-flowing form, such as a powder or granules, optionally mixed with a binder, lubricant, inert diluent, surface active or dispersing agent. Moulded tablets may be made by moulding, in a suitable machine, a mixture of the powdered

active ingredient and a suitable carrier moistened with an inert liquid diluent.

Formulations for rectal administration may be in the form of a suppository incorporating the active ingredient
5 and a carrier such as cocoa butter, or in the form of an enema.

Formulations suitable for parenteral administration conveniently comprise a sterile oily or aqueous preparation of the active ingredient which is preferably isotonic with
10 the blood of the recipient.

Formulations suitable for intra-articular administration may be in the form of a sterile aqueous preparation of the active ingredient which may be in microcrystalline form, for example, in the form of an aqueous micro-
15 crystalline suspension. Liposomal formulations or biodegradable polymer systems may also be used to present the active ingredient for both intra-articular and ophthalmic administration.

Formulations suitable for topical administration
20 include liquid or semi-liquid preparations, such as liniments, lotions, applications; oil-in-water or water-in-oil emulsions, such as creams, ointments or pastes; or solutions or suspensions, such as drops. For example, for ophthalmic administration, the active ingredient may be
25 presented in the form of aqueous eye drops as, for example, a 0.1-1.0% solution.

Formulations suitable for administration to the nose or buccal cavity include powder, self-propelling and spray formulations, such as aerosols and atomizers. The formulations, when dispersed, preferably have a particle size in
30 the range of 10 to 100 μ .

Such formulations are most preferably in the form of a finely comminuted powder for pulmonary administration from a powder inhalation device or self-propelling powder-dis-
35 pensing formulations, where the active ingredient, as a finely comminuted powder, may comprise up to 99.9% w/w of the formulation. In the case of self-propelling solution and spray formulations, the effect may be achieved either by choice of a valve having the desired spray characteristics

(i.e. being capable of producing a spray having the desired particle size) or by incorporating the active ingredient as a suspended powder in controlled particle size. These self-propelling formulations may be either powder-dispensing
5 formulations or formulations dispensing the active ingredient as droplets of a solution or suspension.

Self-propelling powder-dispensing formulations preferably comprise dispersed particles of solid active ingredients, and a liquid propellant having a boiling point
10 below 18°C at atmospheric pressure. The liquid propellant may be any propellant known to be suitable for medicinal administration and may comprise one or more C₁-C₆-alkyl hydrocarbons or halogenated C₁-C₆-alkyl hydrocarbons or mixtures thereof; chlorinated and fluorinated C₁-C₆-alkyl
15 hydrocarbons are especially preferred. Generally, the propellant constitutes 50 to 99.9% w/w of the formulation whilst the active ingredient constitutes 0.1 to 20% w/w, for example about 2% w/w, of the formulation.

The pharmaceutically acceptable carrier in such self-
20 propelling formulations may include other constituents in addition to the propellant, in particular a surfactant or a solid diluent or both. Surfactants are desirable since they prevent agglomeration of the particles of active ingredient and maintain the active ingredient in suspension. Especially
25 valuable are liquid non-ionic surfactants and solid anionic surfactants or mixtures thereof. Suitable liquid non-ionic surfactants are esters and partial esters of fatty acids with aliphatic polyhydric alcohols, for instance, sorbitan monooleate and sorbitan trioleate, known commercially as
30 "Span 80" (Trade Name) and "Span 85" (Trade Name), respectively. The liquid non-ionic surfactant may constitute from 0.01 up to 20% w/w of the formulation, though preferably it constitutes below 1% w/w of the formulation. Suitable solid anionic surfactants include alkali metal, ammonium and amine
35 salts of dialkyl sulphosuccinate (where the alkyl groups have 4 to 12 carbon atoms). The solid anionic surfactants may constitute from 0.01 up to 20% w/w of the formulation, though preferably below 1% w/w of the composition solid diluents may be advantageously incorporated in such self-

propelling formulation where the density of the active ingredient differs substantially from the density of the propellant; also, they help to maintain the active ingredient in suspension. The solid diluent is in the form of a fine powder, preferably having a particle size of the same order as that of the particles of the active ingredient. Suitable solid diluents include sodium chloride, sodium sulphate and sugars.

Formulations of the present invention may also be in the form of a self-propelling formulation wherein the active ingredient is present as such in suspension or in solution. Such self-propelling formulations may comprise the active ingredient, propellant and co-solvent, and advantageously an anti-oxidant stabiliser. The propellant is one or more of these already cited above. Co-solvents are chosen for their solubility in propellant, their ability to dissolve the active ingredient, and for their having the lowest boiling point consistent with these above-mentioned properties. Suitable co-solvents are C_1 - C_6 -alkyl alcohols and ethers and mixtures thereof. The co-solvent may constitute 5 to 40% w/w of the formulation, though preferably less than 20% w/w of the formulation. Antioxidant stabilisers may be incorporated in such solutions-formulations to inhibit deterioration of the active ingredient and are conveniently alkali metal ascorbates or bisulphites. They are preferably present in an amount of up to 0.25% w/w of the formulation.

Such self-propelling formulations may be prepared by any method known in the art. For example, the active ingredient (either as particles as defined hereinbefore as such or in suspension in a suitable liquid or in up to 20% w/v solution in an acceptable co-solvent, as appropriate) is mixed with any other constituents of a pharmaceutically acceptable carrier. The resulting mixture is cooled, introduced in a suitable cooled container, and propellant is added thereto in liquid form; and the container is sealed. Alternatively, such self-propelling formulations may be prepared by mixing the active ingredient either in particles as hereinbefore defined or in 2 to 20% w/v alcohol or aqueous solution as appropriate, together with the remaining

constituents of the pharmaceutically acceptable carrier other than the propellant; introducing the resulting mixture, optionally with some propellant, into a suitable container; and injecting the propellant, under pressure, into the container at ambient temperature through a valve which comprises a part of the container and is used to control release of the formulation from it. Desirably, the container is purged by removing air from it at a convenient stage in the preparation of the self-propelling formulation.

A suitable container for a self-propelling formulation is one provided with a manually-operable valve and constructed of aluminium, stainless steel or reinforced glass. The valve should, of course, be one having the desired spray characteristics of particle size as hereinbefore defined. Advantageously, the valve is of the type which delivers a fixed amount of the formulation on the occasion of each operation of the valve, for example, about 50 to 100 microlitres of formulation in each delivery.

Formulations of the present invention may also be in the form of an aqueous or dilute alcoholic solution, optionally a sterile solution of the active ingredient for use in a nebuliser or atomizer, wherein an accelerated air stream is used to produce a fine mist consisting of small droplets of the solution. A buffering agent and a surface active agent may also be included in such a formulation which should also contain a preservative such as methylhydroxybenzoate.

Other formulations suitable for nasal administration include a fine powder having a particle size of 10 to 100 microns which is administered in the manner in which snuff is taken, i.e. by rapid inhalation through the nasal passage from a container of the powder held close up to the nose.

In addition to the aforementioned ingredients, the formulations of this invention may include one or more additional ingredients, such as diluents, buffers, flavouring agents, binders, surface active agents, thickeners, lubricants, preservatives, e.g. methylhydroxybenzoate (including anti-oxidants), emulsifying agents and

the like.

The compositions may further contain other therapeutically active compounds usually applied in the treatment of the above mentioned pathological conditions, for instance
5 glucocorticoids, anti-histamines, platelet activating factor (PAF) antagonists, anticholinergic agents, methyl xanthines, β -adrenergic agents, salicylates, indomethacin, flufenamate, naproxen, timegadine, gold salts, penicillamine, serum
10 cholesterol-reducing agents, retinoids, zinc salts, and salicylazosulfapyridin (Salazopyrin).

According to the invention, the present compounds are administered to a patient suffering from one of the above mentioned pathological conditions in a daily dose (for
adults) from 0.1 mg to 7000 mg, preferably from 35 - 3500
15 mg, and in the veterinary practice correspondingly in daily doses from 0.5 to 100 mg/kg bodyweight.

The invention will now be further described in the following non-limiting Examples:

20 Example 1

3-(2'-Quinolylmethoxy)-N-(3"-carboxymethoxybenzyl)aniline

To a solution of 3-(2'-quinolylmethoxy)aniline (2.5 g, 10 mmole) in methanol (100 ml), 3-formylphenoxy-
acetic acid (2.0 g) is added, and the mixture is stirred at
25 ambient temperature for 1 hour. The precipitated 3-(2'-
-quinolylmethoxy)-N-(3"-carboxymethoxybenzylidene)aniline is collected by filtration, washed with a minor amount of methanol and with diethyl ether and dried in air. It is then
suspended in ethanol (200 ml), and sodium borohydride (1.5
30 g) is added in portions during 1 hour, while stirring at ambient temperature. The resulting mixture is filtered through filter aid and evaporated in vacuo. The residue is treated with water, and the resulting solution is neutralized to pH 7.0 using dilute acetic acid. It is then
35 extracted twice with ethyl acetate (about 150 ml), and the organic layer is separated, dried (MgSO_4) and evaporated in vacuo to give the title compound, which after recrystallization from ethanol is obtained with a melting point of 122-124°C dec.

Examples 2-16

By following the procedure of Example 1 and using the appropriate starting materials, compounds of Table I are obtained.

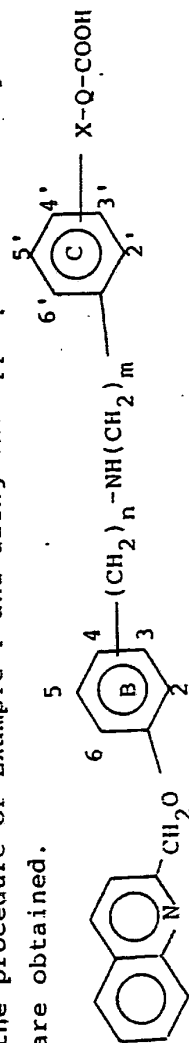


Table I:

Ex. No.	Position of bond in ring B	Position of bond in ring C	n	m	X	Q	Melting point	Remarks
2	3	2'	1	0	bond	bond	168-170°C	hydrate
3	3	3'	1	0	bond	bond	166-168°C	sodium salt, dihydrate
4	3	4'	1	0	bond	bond	180-182°C	dihydrate
5	4	4'	1	0	bond	bond	> 240°C	hydrate
6	3	4'	1	1	bond	bond	175-177°C	sodium salt, dihydrate
7	4	4'	1	1	bond	bond	225-227°C	hydrate
8	3	4'	1	0	bond	-CH ₂ -	138-140°C	hydrate
9	3	2'	0	1	oxygen	-CH ₂ -	151-152°C	sodium salt, trihydrate
10	3	4'	0	1	oxygen	-CH ₂ -	195-235°C	hydrate
11	3	2'	0	1	oxygen	-(CH ₂) ₂ -	80-85°C	dihydrochloride, hydrate
12	3	4'	0	1	oxygen	-CH(CH ₃)-	187-189°C	dihydrochloride, hydrate
13	4	2'	0	1	oxygen	-CH(CH ₃)-	175-179°C	dihydrochloride, hydrate
14	3	2'	0	1	oxygen	-(CH ₂) ₃	137-138°C	hydrate
15	3	3'	0	1	oxygen	-(CH ₂) ₃	160-162°C	dihydrochloride H ₂ O
16	3	4'	0	1	oxygen	-(CH ₂) ₃	155-170°C	dihydrochloride, hemi-hydrate

Example 173-(2'-Quinolylmethoxy)-N-(4"-(1H-tetrazolyl)benzyl)aniline

A mixture of 3-(2'-quinolylmethoxy)-N-(4"-cyano-benzyl)aniline (0.75 g, 2 mmole), sodium azide (0.5 g), ammonium chloride (0.2 g) and dimethyl formamide (15 ml) is stirred at 120°C for 5 hours. The resulting mixture is, after cooling, carefully poured into a mixture of ice and water, whereafter an excess of dilute acetic acid is added to precipitate the title compound. It is collected by filtration and dissolved in an equimolar amount of dilute potassium hydroxide. After evaporation in vacuo and reevaporation several times with ethanol, the residue is triturated with isopropanol to give the potassium salt of the title compound as a dihydrate having a melting point higher than 250°C.

Example 183-(2'-Quinolylmethoxy)-N-(3"-(1H-tetrazolyl)benzyl)aniline

By following the procedure of Example 17, but replacing 3-(2'-quinolylmethoxy)-N-(4"-cyanobenzyl)aniline with 3-(2'-quinolylmethoxy)-N-(3"-cyanobenzyl)aniline, the title compound is obtained as a hydrate with a melting point of 116-118°C.

Example 193-(2'-Quinolylmethoxy)-N-(4"-(1H-tetrazolyl)(3-propyloxy)-benzyl)aniline

By following the procedure of Example 17, but replacing 3-(2'-quinolylmethoxy)-N-(4"-cyanobenzyl)aniline with 3-(2'-quinolylmethoxy)-N-(4"-cyano(3-propyloxy)benzyl)-aniline, the title compound is obtained as a dihydrate of the dihydrochloride with a melting point of 115-117°C.

Example 203-(2'-Quinolylmethoxy)-N-(3"-fluorobenzyl)-N-(4'''-hydrox-aminocarbonylbenzyl)aniline

A mixture of 3-(2'-quinolylmethoxy)-N-(3"-fluoro-benzyl)-N-(4'''-carbomethoxybenzyl)aniline (2.4 g, 4.7

mmole), hydroxylamine hydrochloride (1.4 g, 20 mmole), 6.2 N potassium hydroxide (5 ml) and methanol (25 ml) is stirred at ambient temperature for about 48 hours. The resulting solution is then acidified using 4N acetic acid to
5 precipitate the title compound which is obtained as a hemihydrate with a melting point of 157-160°C.

Example 21

3-(2'-Quinolylmethoxy)-N-(2"-hydroxaminocarbonylphenyl)-
10 aniline

By following the procedure of Example 20, but replacing 3-(2'-quinolylmethoxy)-N-(3"-fluorobenzyl)-N-(4'''-carbomethoxybenzyl)aniline with 3-(2'-quinolylmethoxy)-N-(2"carbethoxyphenyl)aniline, the title compound
15 is obtained with a melting point of 184-187°C.

Example 22

4-(2'-Quinolylmethoxy)-N-(2"-carboxymethoxybenzyl)-aniline

By following the procedure of Example 1, but
20 replacing 3-(2'-quinolylmethoxy)aniline with 4-(2'-quinolylmethoxy)aniline and 3-formylphenoxyacetic acid with 2-formylphenoxyacetic acid, the title compound is obtained as a dihydrochloride, pentahydrate with a melting point 215-217°C.

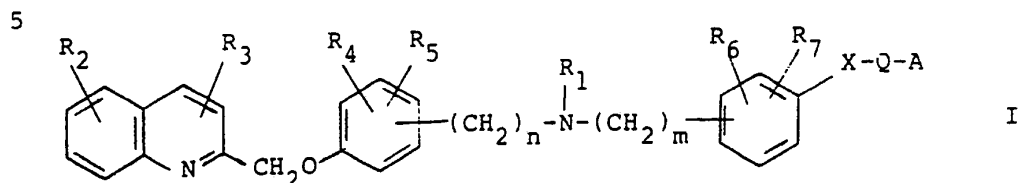
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WHAT WE CLAIM IS:

1. A compound of the formula I



- 10 in which formula I R_1 stands for hydrogen, straight or branched, saturated or unsaturated, unsubstituted or substituted C_1 - C_8 -alkyl, aryl or for ar- C_1 - C_4 -alkyl, aryl or ar being unsubstituted or substituted phenyl, the above substitution being one or more of the following substituents:
- 15 halogen, pseudo halogen, such as trifluoro methyl, cyano, nitro, amino, substituted amino, carboxy, carbalkoxy, carbamyl, hydroxy, alkyl, alkoxy; R_2 , R_3 , R_4 , R_5 , R_6 and R_7 are the same or different and stand for hydrogen, halogen, pseudo halogen, cyano, nitro, amino, substituted amino,
- 20 carboxy, carbalkoxy, carbamyl, hydroxy, alkyl, alkoxy; n and m are the same or different and stand for an integer from 0-6; provided that n cannot be zero when A stands for carboxy and X and Q both stand for a bond; X stands for a bond or for O, S, S(O), S(O)₂ or for NR₈ where R₈ is defined
- 25 as R_1 above; Q stands for a bond or for straight or branched, C_1 - C_6 alkylene; A stands for an acidic group, e.g. for carboxy, 1H-tetrazolyl, a sulphonic acid group, a sulfamyl group, a sulphinic acid group or a hydroxamic acid group, and pharmaceutically acceptable, non-toxic salts and
- 30 in-vivo hydrolyzable esters thereof.

2. A compound according to formula I of claim 1, in which -X-Q-A stands for a carboxy- C_1 - C_6 -alkoxy or a 1H-tetrazolyl group.

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3. A salt according to claim 1, in which the salt is

selected from the group consisting of salts formed with hydrochloric, hydrobromic and hydroiodic acid, phosphoric acid, sulphuric acid, nitric acid, p-toluenesulphonic acid, methanesulphuric acid, formic acid, acetic acid, propionic acid, citric acid, tartaric acid, and maleic acid, and alkali metal salts and alkaline earth metal salts, such as lithium, sodium, potassium, magnesium, calcium salts, as well as salts with ammonia and suitable non-toxic amines, such as C₁-C₆alkylamines, e.g. triethylamine, C₁-C₆-alkanolamines, e.g. diethanolamine or triethanolamine, procaine, cycloalkylamines, e.g. dicyclohexylamine, benzylamines, e.g. N-methylbenzylamine, N-ethylbenzylamine, N-benzyl-β-phenethylamine, N,N'-dibenzylethylenediamine or dibenzylamine, and heterocyclic amines, e.g. morpholine and N-ethylpiperidine.

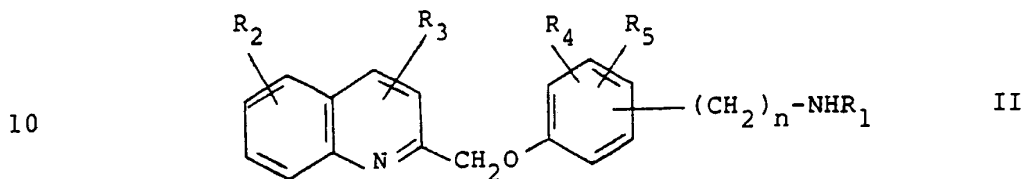
4. A compound of claim 1 which is selected from the group consisting of
3-(2'-quinolylmethoxy)-N-(3"-carboxymethoxybenzyl)aniline;
20 3-(2'-quinolylmethoxy)-N-(2"-carboxymethoxybenzyl)aniline;
3-(2'-quinolylmethoxy)-N-(4"-carboxymethoxybenzyl)aniline;
3-(2'-quinolylmethoxy)-N-(4"-(1-carboxyethoxy)benzyl)-aniline;
3-(2'-quinolylmethoxy)-N-(2"-carboxy-(3-propyloxy)benzyl)-
25 aniline;
3-(2'-quinolylmethoxy)-N-(4"-(1H-tetrazolyl)benzyl)aniline;
3-(2'-quinolylmethoxy)-N-(3"-(1H-tetrazolyl)benzyl)aniline
3-(2'-quinolylmethoxy)-N-(4"-(1H-tetrazolyl)(3-propyloxy)-benzyl)aniline;
30 3-(2'-quinolylmethoxy)-N-(3"-fluorobenzyl)-N-(4'''-hydroxaminocarbonylbenzyl)aniline.

5. A pharmaceutical preparation, containing a compound according to any one of claims 1 - 4 alone or together with
35 the necessary auxiliary agents.

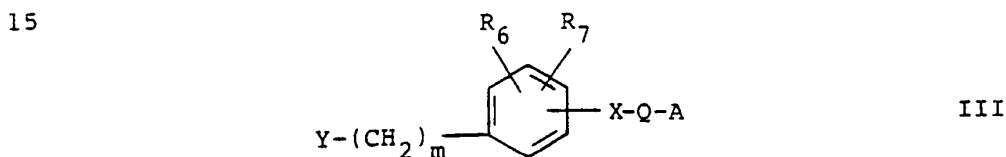
6. A method of treating patients in need of treatment characterized in administering to said patients an effective amount of one or more compounds according to any of claims

1 - 4, if necessary together or in combination with one or more other therapeutically active components.

7. Method for producing a compound of formula I according to claim 1, in which
- a) an amine of the formula II

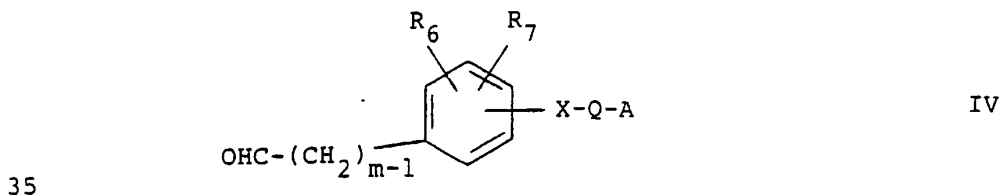


in which R_1 , R_2 , R_3 , R_4 , R_5 and n have the meanings defined in claim 1, is reacted with a compound of the formula III



- 20 in which R_6 , R_7 , X , Q , A and m have the above meanings defined in claim 1, and Y is capable of forming a "good leaving group", such as chlorine, bromine or iodine, an alkyl- or arylsulphonyloxy group, an alkylsulphate group, a chlorosulphonyloxy group, an alkylsulphite group, a mono- or
- 25 dialkylphosphate group or a nitrate group, to form a compound of the formula I; or

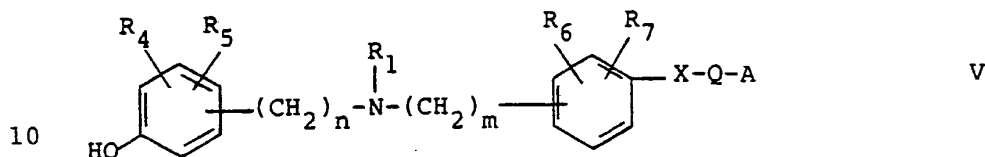
- b) an amine of the formula II in which R_1 stands for hydrogen is converted to a compound of the formula I, in which R_1 stands for hydrogen by reductive alkylation, e.g.
- 30 by reaction with a carbonyl compound of the formula IV



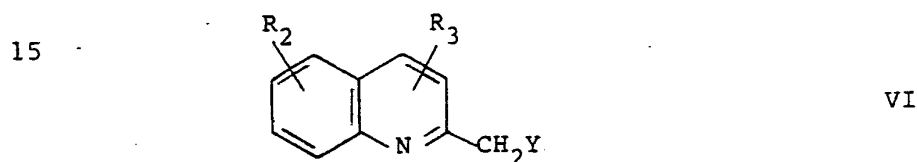
in which R_6 , R_7 , X , Q , A and m have the above meanings, followed by hydrogenation in the presence of a suitable catalyst or by reduction e.g. with an alkalimetal boro-

hydride, the hydrogenation or reduction, if convenient, being performed simultaneously with the reaction with the carbonyl compound, that is, without isolation of the intermediary, so called Schiff-base to form the desired compound of formula I; or

c) a compound of the formula V

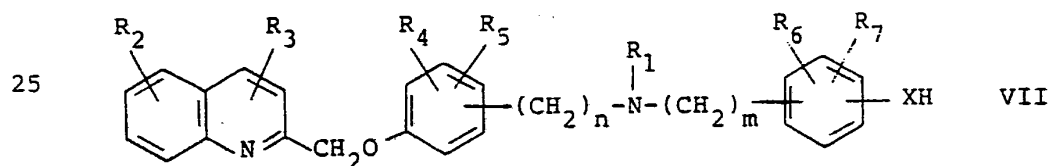


in which R_1 , R_4 , R_5 , R_6 , R_7 , X , Q , A , n and m have the above meanings, is reacted with a compound of the formula VI



20 in which R_2 , R_3 and Y have the above meanings, to form the desired compound of formula I; or

d) a compound of the formula VII

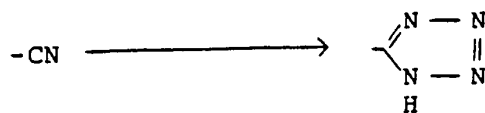


30 in which R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , R_7 , n and m have the above meanings, and X stands for O , S or NHR_8 , where R_8 has the above meanings, is reacted with a compound of the formula VIII

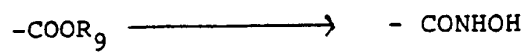


35 in which A , Q , and Y have the above meanings, to form the desired compound of formula I;

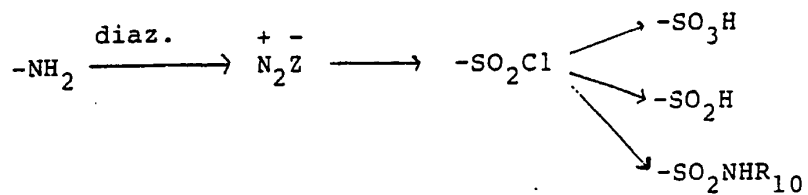
the acidic functionalities optionally being prepared according to the following general reaction schemes:



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R₁₀ having the same meanings as R₁.

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INTERNATIONAL SEARCH REPORT

International Application No PCT/DK88/00188

I. CLASSIFICATION F SUBJECT MATTER (if several classification symbols apply, indicate all) *		
According to International Patent Classification (IPC) or to both National Classification and IPC ⁴ C 07 D 215/12, 215/14, 215/18, 215/20, 215/22, 215/24, 215/26, 215/32, 215/38, 215/40, 215/42, C 07 D 401/12		
II. FIELDS SEARCHED		
Minimum Documentation Searched ⁷		
Classification System	Classification Symbols	
IPC 4	C 07 D	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ⁸		
SE, NO, DK, FI classes as above		
III. DOCUMENTS CONSIDERED TO BE RELEVANT ⁹		
Category *	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
A	EP, A2, 0 190 722 (USV PHARMACEUTICAL CORPORATION) 13 August 1986 see pages 1-2, the claims	1-5, 7
A	EP, A3, 0 206 751 (MERCK FROSST CANADA INC.) 30 December 1986 see examples 85, 86, the claims	1-5, 7
A	EP, A2, 0 219 307 (MERCK FROSST CANADA INC.) 22 April 1987 see the whole document	1-5, 7
A	EP, A3, 0 219 308 (MERCK FROSST CANADA INC.) 22 April 1987 see particularly page 4	1-5, 7
A	EP, A2, 0 232 954 (AMERICAN HOME PRODUCTS CORPORATION) 19 August 1987 see particularly pages 3-5, the claims	1-5, 7
.../...		
<p>* Special categories of cited documents: ¹⁰</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"G" document member of the same patent family</p>		
IV. CERTIFICATION		
Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report	
1989-03-08	1989-03-08	
International Searching Authority	Signature of Authorized Officer	
Swedish Patent Office	Eva Johansson	

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)		
Category*	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No
A	EP, A2, 0 233 763 (MERCK FROSST CANADA INC.) 26 August 1987 see particularly pages 14-17, the claims	1-5, 7
A	EP, A2, 0 271 287 (MERCK FROSST CANADA INC.) 15 June 1988 see particularly pages 18-19, the claims	1-5, 7
A	DE, A1, 36 07 382 (LEO PHARMACEUTICAL PRODUCTS LTD. A/S) 11 September 1986 see pages 9-10, the claims	1-5, 7

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. ☒ OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE ¹

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. ☒ Claim numbers 6 because they relate to subject matter not required to be searched by this Authority, namely:

A method of treating patients...

2. ☐ Claim numbers because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claim numbers because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. ☐ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING ²

This International Searching Authority found multiple inventions in this international application as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.
2. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

- ☐ The additional search fees were accompanied by applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.